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US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 481

HEMODYNAMIC ALTERATIONS DUE TO SALMONELLA TYPHOSA ENDOTOXIN WITH SPECIAL REFERENCE TO THE CORONARY VASCULAR BED

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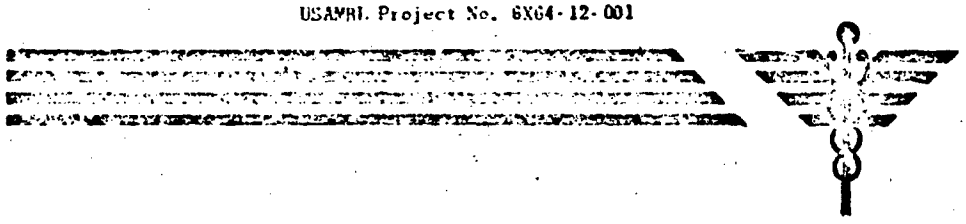
Cold Injury Studies
Task 08
Environmental Medicine
USAMRL Project No. 6X64-12-001



UNITED STATES ARMY
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HEMODYNAMIC ALTERATIONS DUE TO SALMONELLA TYPHOSA ENDOTOXIN WITH SPECIAL REFERENCE TO THE CORONARY VASCULAR BED

I. INTRODUCTION

The general physiological and more detailed hemodynamic alterations produced in animals by bacterial endotoxins have been reviewed by Thomas (1) and Gilbert (2). It has been shown that following the administration of endotoxin there is a fall in cardiac output which is accompanied by a decrease in auricular filling. Despite the extensive literature on the hemodynamic effects produced by endotoxin in various vascular beds, little attention has been given to the study of its action on the coronary circulation.

In Gilbert's review (2), it was held that there was "no evidence to date to support the view that endotoxin had any important effect on myocardial function." More recently, however, Maxwell and his associates (3) demonstrated by catheterization techniques that there was a decrease in the coronary blood flow and cardiac efficiency associated with an increase in myocardial oxygen utilization following endotoxin. There was, however, no significant change in the calculated resistance to flow through the coronary vascular bed.

This paper reports changes in resistance to flow through the coronary vascular bed of the dog produced by local administration of the endotoxin of Salmonella typhosa 0901. Resistance was calculated from measurement of coronary perfusion pressure with the rate of blood flow to the coronary vascular bed held constant. The heart was beating but performing no external work.

II. MATERIALS AND METHODS

The study included a total of 20 mongrel dogs ranging in weight from 10 to 18 kg. The animals were anesthetized with sodium pentobarbital (35 mg/kg), and artificially ventilated through a tracheal cannula. The heart was exposed through the right fourth intercostal space. Heparin sodium (5 mg/kg) was injected intravenously and plastic cannulae were introduced into the superior and inferior venae cavae by way of the right atrium (Fig. 1, page 2). A rotating disc oxygenator,[1]

[1] Kay-Cross disc oxygenator, Pemco Inc., Cleveland 31, Ohio.

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ABSTRACT

HEMODYNAMIC ALTERATIONS DUE TO SALMONELLA TYPHOSA ENDOTOXIN WITH SPECIAL REFERENCE TO THE CORONARY VASCULAR BED

OBJECT

The experiments were designed to determine the effect of gram-negative bacterial endotoxin on the coronary vascular bed of the dog.

RESULTS

When endotoxin was injected into the coronary arteries of the beating, non-perfusing dog heart under conditions of constant coronary blood flow, there was a progressive decrease in the coronary vascular resistance and total peripheral resistance.

CONCLUSIONS

This study provides evidence which indicates that gram-negative bacterial endotoxins can exert an important effect on coronary vascular resistance and total peripheral resistance.

RECOMMENDATIONS

The effect of endotoxin on coronary vascular resistance should be studied in the denervated, regitimized, and antihistamine treated dog heart to ascertain more precisely the mode of action of endotoxin on the coronary vasculature.

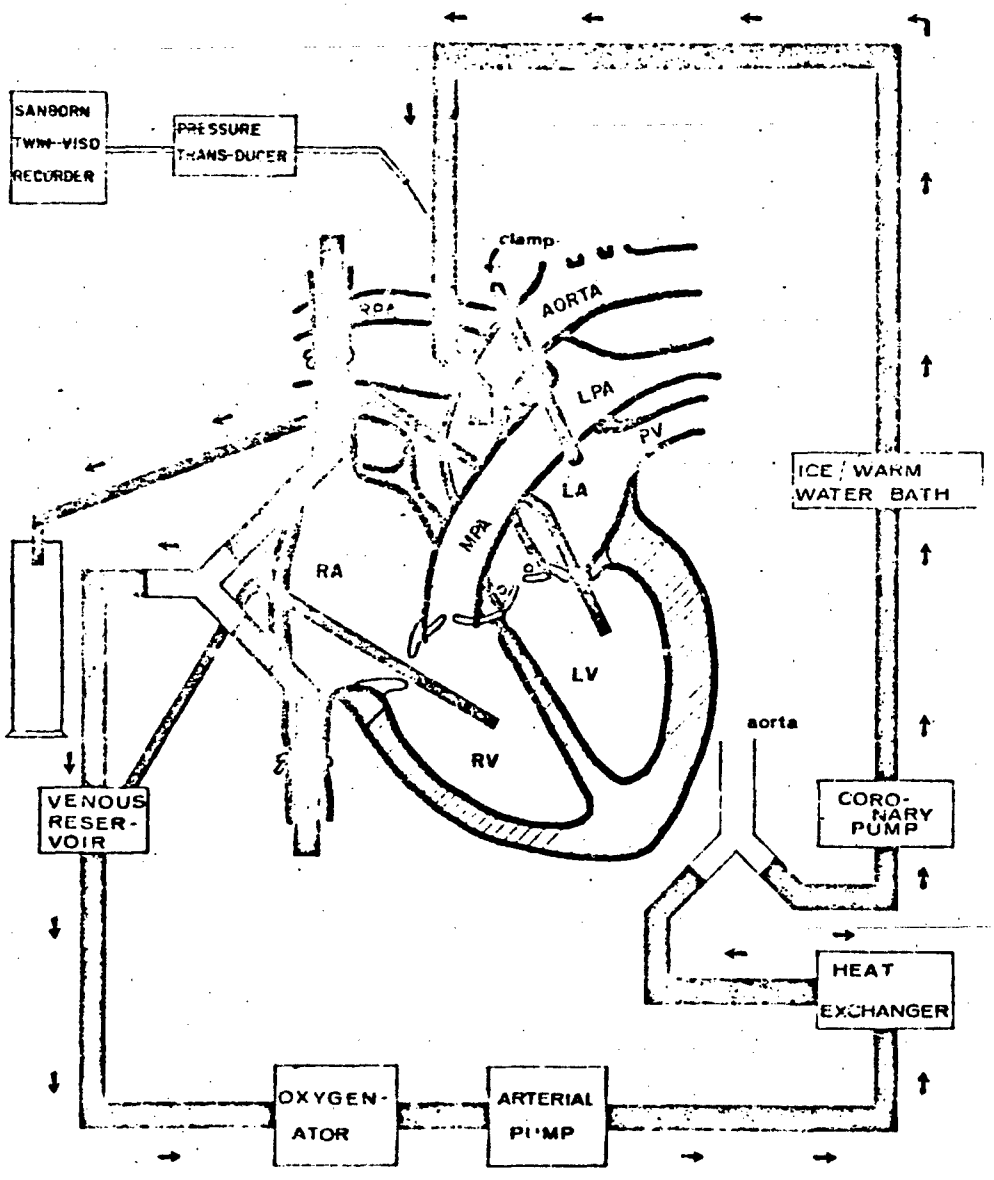

Fig. 1. Schematic diagram of the cardio-pulmonary bypass and coronary perfusion systems.

blood heat exchanger,[2] and blood pump[3] were interposed between the cannulae and the left femoral artery, and the body was perfused with oxygenated blood a. 37°C, at the rate of 80 to 90 ml/kg/min. At this point in the procedure positive pressure respiration was terminated. Coronary venous blood was collected from the right side of the heart with a cannula threaded through the tricuspid valve and this blood was returned to the venous limb of the perfusion circuit. Left heart blood (from arterioluminal, Thebesian, and bronchial vessels) was collected with another cannula inserted into the left atrium and left ventricle through a superior pulmonary vein.

The coronary vascular bed was perfused at a constant flow rate with a second pump[4] interposed between the right femoral artery and the ascending aorta (Fig. 1). After setting the pump in motion, the aorta and pulmonary artery were cross-clamped approximately 3 cm from the heart.[5] This diverted the output of the pump through the entire coronary vascular bed. Hence, coronary perfusion was never interrupted. Perfusion pressure was measured with a resistance wire pressure transducer. The external carotid artery was needled for measurement of systemic arterial pressure. The electrocardiogram was recorded throughout the experiment.

In ten dogs, 0.6 mg/kg of purified lipopolysaccharide (endotoxin) from S. typhosa 0901[6] was injected in one bolus of fluid, usually less than 2 ml, into the coronary perfusion circuit. Coronary perfusion pressure and systemic arterial pressure were monitored over the succeeding 30 minutes with a two-channel direct writing recorder.[7] In a second series of ten dogs, 1 ml of pyrogen-free water was injected into the coronary perfusion circuit and pressures were likewise recorded for the subsequent 30 minute period.

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[2]Blood Heat Exchanger, Ward Laboratories, Durham, North Carolina.

[3]Sigmamotor Pump, Model T-65, Sigmamotor Inc., Middleport, New York.

[4]Sigmamotor Pump, Model T-6, Sigmamotor Inc., Middleport, New York. The pump was independent of pressure over the ranges encountered and was pre-calibrated to deliver ten different rates of flow.

[5]Post-mortem tests showed the aortic valves to be competent to pressures in excess of those encountered.

[6]Bacto Lipoplysaccharide, Difco Laboratories, Inc., Detroit 1, Michigan.

[7]Sanborn Model 60, Twin-Viso, Sanborn Company, Waltham, Massachusetts.

In five of the ten experimental animals, blood was simultaneously withdrawn from the coronary artery, coronary vein, and pump-oxygenator before and 30 minutes following the injection of endotoxin. These blood samples were analyzed for oxygen and carbon dioxide content, serum sodium and potassium concentrations, hematocrit and hemoglobin concentration by the Van Slyke manometric method, flame photometry, microcapillary centrifugation, and photometric method, respectively.

Since vena cava and right heart pressures remained atmospheric, the resistance to flow through the coronary vascular bed and systemic circulation were calculated by dividing perfusion pressure by the rate of blood flow and was expressed as mm Hg/ml/min.

The proportion of time spent by the ventricles in systole was estimated by using the following formula: per cent of time spent in systole = $\frac{\text{QT interval} \times \text{number beats per min}}{60} \times 100$.

At the conclusion of the experiments the animals were sacrificed and subjected to gross and microscopic pathologic examination.

III. RESULTS

Coronary arterial pressure and resistance. There was no significant change in the coronary arterial pressure and resistance in the control animals given pyrogen-free water (Fig. 2). Following the injection of endotoxin (Fig. 2) coronary arterial pressure progressively decreased in nine dogs and remained essentially unchanged in one. The average arterial resistance prior to the administration of endotoxin was 0.95 mm Hg/ml/min, and resistance values at 5, 10, 15, 20, 25, and 30 minutes following endotoxin were 0.91, 0.89, 0.81, 0.75, and 0.71 mm Hg/ml/min, respectively. The average resistance at 30 minutes was 25 per cent less than the average control value ($p < 0.01$).

Systemic arterial pressure and resistance. There was no change in the systemic arterial pressure or calculated resistance in the control animals given pyrogen-free water (Fig. 3, page 6). Systemic arterial pressure decreased in nine animals and remained essentially unchanged in one dog following administration of endotoxin (Fig. 3). The average control pressure was 65 mm Hg. Thirty minutes after endotoxin, the pressure had fallen to an average of 47 mm Hg. This represented a 29 per cent decrease in total peripheral resistance ($p < 0.01$).

Electrocardiographic changes. The effect of endotoxin upon heart rate and QT interval were of importance because they permitted an

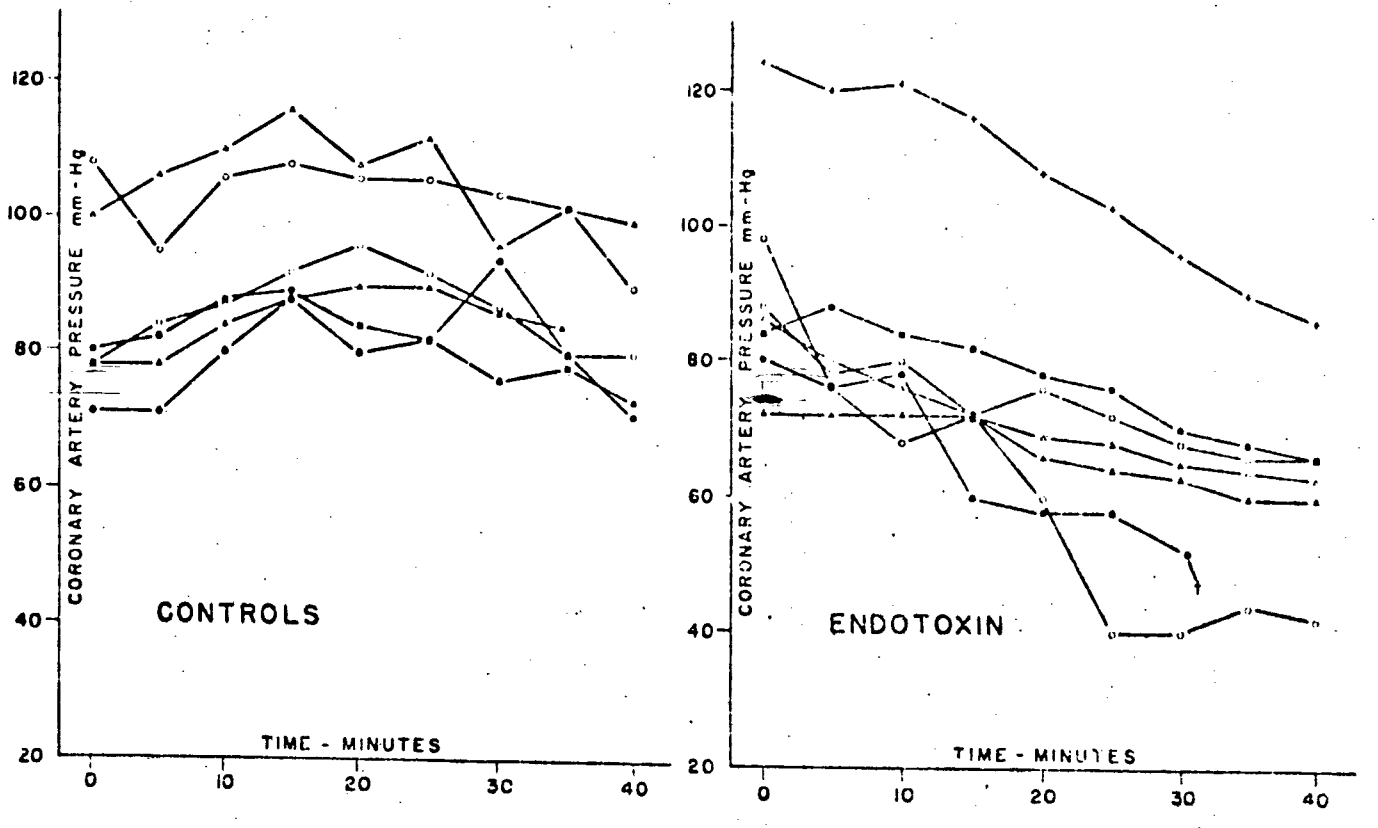

Fig. 2. (left) The effect of 1 ml of pyrogen-free water on the coronary vascular pressure in ten control animals. Heavy line represents the mean pressures. Coronary blood flow (average) 102 ml/min. (right) The effect of S. typhosa endotoxin (0.6 mg/kg) on the coronary vascular pressure in ten experimental animals. Heavy line represents the mean pressures. Coronary blood flow (average) 98 ml/min.

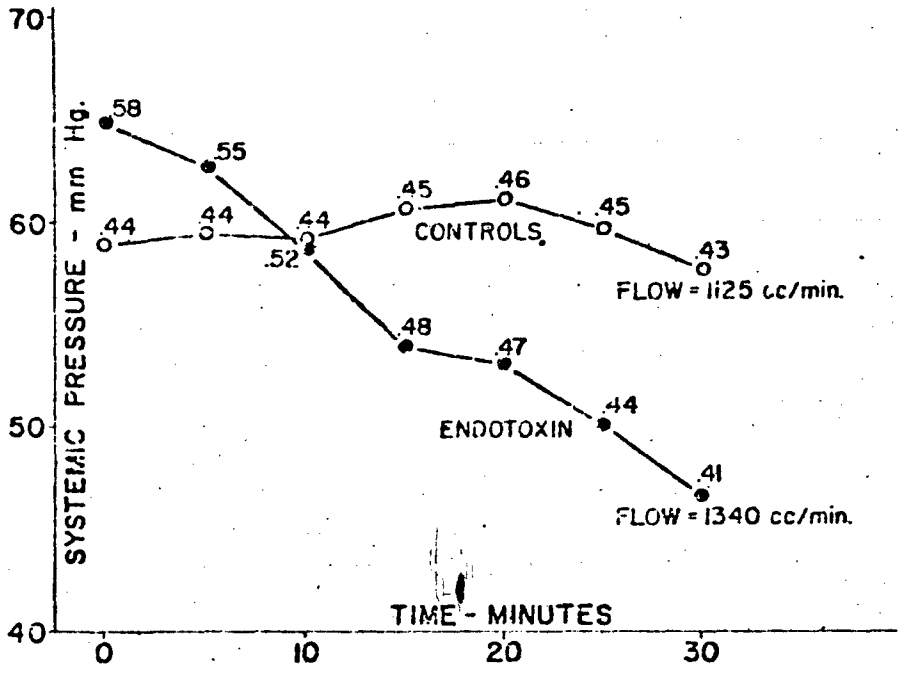

Fig. 3. Systemic vascular pressure changes in ten experimental animals following administration of S. typhosa endotoxin (0.6 mg/kg) and in ten control animals following administration of 1 ml of pyrogen-free water. Numbers represent calculated values for total peripheral resistance.

inference to be made regarding coronary vascular transmural pressure. Using the QT interval and heart rate it was found that there was no significant difference in the per cent of time and ventricles spent in systole (Table I). The electrocardiograms of those animals given endotoxin revealed non-specific T-wave abnormalities and premature ventricular contractions. Two dogs developed complete heart block concomitantly with massive intrapleural hemorrhages. Another animal developed intermittent runs of various types of intraventricular conduction defects. These latter animals had myocardial hemorrhages.

Myocardial metabolism. There were no significant changes in arterial and venous hematocrit, in the concentrations of sodium and potassium, and hemoglobin following endotoxin. The A-V difference for oxygen and carbon dioxide both increased slightly (0.8 volumes per cent and 1.8 volumes per cent, respectively) but neither increase was statistically significant (Table II).

TABLE I

THE EFFECT OF INTRAPERITONEAL INJECTION OF ENDOTOXIN AND PYROGEN-FREE WATER ON THE PER CENT OF TIME SPENT BY THE VENTRICLES IN SYSTOLE*

	CONTROL					ENDOTOXIN			
Dog No.	Heart Rate		Per Cent Time in Systole		Dog No.	Heart Rate		Per Cent Time in Systole	
	0 min	30 min	0 min	30 min		0 min	30 min	0 min	30 min
1	150	150	69	67	1	135	140	56	51
2	130	140	74	70	2	140	140	56	56
3	120	130	40	39	3	140	130	65	68
4	150	100	45	46	4	120	200	40	46
5	80	65	43	43	5	140	140	51	51
6	120	130	56	56	6	140	70	51	39
7	140	135	65	67	7	160	160	64	64
8	100	60	53	53	8	107	55	43	32
9	120	130	48	47	9	165	155	69	72
10	140	130	65	66	10	140	130	70	72
Average	126	117	56	55		138	132	56	55

*Calculation: per cent of time spent in systole = $\frac{\text{QT interval} \times \text{heart rate}}{60} \times 100$

TABLE II

CORONARY OXYGEN CONSUMPTION AND CARBON DIOXIDE PRODUCTION IN DOGS TREATED WITH SALMONELLA TYPHOSA ENDOTOXIN

	A-V Oxygen			A-V Carbon Dioxide		
Dog No.	Control	Exptl.	Dif.	Control	Exptl.	Dif.
4	9.9*	9.8	-0.1	10.1	10.9	0.8
5	7.0	7.3	0.3	6.4	6.6	0.2
6	8.9	9.4	0.5	3.0	5.3	2.3
7	2.5	4.0	1.5	1.7	6.8	5.1
8	6.6	8.2	1.6	5.2	6.0	0.8
Average	7.0	7.8	0.8	5.3	7.1	1.8

*Volume per cent.

Post-mortem examinations. Free blood was found at autopsy in all body cavities of animals treated with endotoxin. There was passive congestion in the liver and spleen. The mucous membranes of the gall bladder, stomach, and spleen were edematous and hemorrhagic. Omental vessels were markedly dilated. Glandular tissues, including the spleen, pancreas, adrenals, and testes were hemorrhagic and congested. There were areas of hemorrhage and petechiae over the surface of the heart There were no abnormalities of these types found on examination of animals injected with pyrogen-free water.

IV. DISCUSSION

These studies show that the injection of the endotoxin of S. typhosa 0901 into the coronary vascular bed of the dog perfused at a constant flow results in a progressive decrease in coronary vascular resistance. This resistance decrease probably results from active vasodilation either due to a direct effect of the endotoxin on vascular smooth muscle or to an indirect effect through some remote action of the endotoxin.

A decrease in vascular resistance can be due either to vasodilatation or a decrease in blood viscosity. However, since hematocrit and temperature remained unchanged throughout the experiments, resistance changes due to viscosity seem unlikely. It is highly improbable that the observed resistance changes were due to the effects of viscosity as influenced by the non-Newtonian character of blood, since both pressures and flow rates were within physiological limits (4).

The electrocardiographic measurements suggested that the decrease in vascular resistance was due to active vasodilatation evoked by changes in the tone of smooth muscle rather than by changes in coronary transmural pressure. Since there was no significant decrease in the time spent by the ventricles in systole (calculated from the QT interval and heart rate), it may be inferred that the extraluminal intramyocardial pressure did not change. With no change in the extraluminal pressure the observed decrease in resistance must have resulted from active vasodilatation. Even though the amount of endotoxin given was less than that used in previous studies, it is likely that because the endotoxin was injected directly into the coronary arteries, the concentration achieved in the myocardium was higher. Endotoxin, therefore, has an effect on the coronary vascular bed.

Gilbert (2) suggests that the effect of endotoxin on resistance within individual vascular beds may be more important than its overall effect on the total peripheral resistance. Studies have been reported on several vascular beds including the liver (5), intestine (6), lung (7), kidney (8), and forelimb (9, 10). These studies indicate that there are two phases of the vascular response to endotoxin--an early, transitory phase of increased resistance and a longer phase of lowered resistance. Contrary to these studies, we were unable to demonstrate an increase in vascular resistance in the early phase. There was a progressive decrease in resistance over the entire 30 minutes of the experiment. Whether the decreased resistance was due to a direct action of the endotoxin on the vascular bed or was secondary to a release of vasoactive substances could not be determined during these experiments. A previous study

reported from this laboratory (11) has shown that slight increases in local serum potassium actively dilate the coronary vascular bed of the dog. There was, however, no detectable change in serum potassium following endotoxin in this study.

It has been suggested (5, 12) that hypotension induced by endotoxin is primarily brought about by a diminished venous return and that calculated total peripheral resistance may even rise following the administration of endotoxin (13). Hinshaw and his associates (14), on the other hand, have demonstrated a significant fall in total peripheral resistance in eviscerated and noneviscerated dogs following the administration of endotoxin. Utilizing a similar technique, the 29 per cent fall in total peripheral resistance demonstrated in our experiments is in close agreement with the 23 per cent reduction in total peripheral resistance reported by Hinshaw et al. In both studies control animals demonstrated no significant change in total peripheral resistance. The progressive decrease in the blood level in our oxygenator during studies involving the use of endotoxin indicated that there was a significant amount of vascular pooling. These results indicate that hypotension induced by endotoxin may be brought about by both a peripheral venous pooling of blood with a consequent diminished return to the heart, as well as by a decrease in arteriolar tone.

The impression of Maxwell and his associates (3) that the increased uptake of oxygen by the myocardium was due to decreased blood flow appears to be substantiated by our results. When the blood flow remained unchanged, as in this study, no significant change in the myocardial oxygen uptake was observed.

V. SUMMARY AND CONCLUSIONS

Under the conditions of these experiments (constant coronary blood flow in a beating, non-perfusing heart) the administration of 0.6 mg/kg of S. typhosa endotoxin directly into the coronary arteries resulted in a progressive decrease in coronary vascular resistance and total peripheral resistance.

The observed decreases in coronary vascular and total peripheral resistances appeared to be due to active vasodilatation.

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